No. 22-56014

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

UNITED STATES,

Appellant,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., et al.,

Appellees.

On Appeal from the United States District Court for the
Central District of California
Hon. Jesus G. Bernal, No. EDCV 18-1005 JGB

ANSWERING BRIEF

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, California Stem Cell Treatment Center, Inc., and Cell Surgical Network state that they have no parent corporation, and that no corporation owns 10% or more of their stock.

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INTRODUCTION

Appealing from judgment following a seven-day bench trial, the United States argues that the Food and Drug Administration ("FDA") may use the Food, Drug, and Cosmetic Act ("FDCA") to regulate surgeons who use a patient's cells parts to treat disease. The government's position strains the FDCA's definition of "drugs" beyond logic to encompass surgical procedures traditionally regulated by the states. As the district court held, physicians practice medicine when they use a patient's own cells and tissues to treat and cure disease and this practice is outside the FDA's jurisdiction. And even if the FDA had jurisdiction, the outpatient surgical procedure Appellees perform here—removing, isolating, and reimplanting a patient's own stem cells during the same surgical procedure—is exempted from regulation by the so-called "Same Surgical Procedure" or "SSP" exception.

Congress enacted the FDCA in 1938 to safeguard consumers from impure and unproven drugs before they could be mass marketed. The FDCA's requirements ensure that drugs with a constant chemical composition are tested and manufactured under standardized conditions before being released downstream for use. But the FDCA's "drug"

requirements do not apply to the surgical suite. It is implausible to think that the 1938 Congress expected surgeons to pause during a venous bypass surgery to test a vein's expiration date or to measure the vein's active ingredients and weight. And, indeed, the legislative history is replete with statements that Congress did *not* intend for the FDCA to interfere with the practice of medicine.

The government's contrary position is predicated on a perfunctory reading of the term "drug," arguing it includes all articles intended for the treatment or prevention of disease. But in the last few years, the Supreme Court repeatedly has insisted that jurisdictional grants of authority to federal agencies cannot be read mechanically. Where, as here, a federal agency asserts jurisdiction over an area traditionally regulated by the states (the practice of medicine) and seeks to intrude on fundamental individual liberties (the right to determine what shall be done with one's own body), the agency must point to unmistakably clear statutory language. The FDCA's opaque definition of "drugs" is far too slender a reed on which to predicate federal jurisdiction over the surgical suite.

Even if the FDA's jurisdictional argument were colorable, Appellees' outpatient surgical procedure would be exempted from regulation by the

SSP exception. The SSP exception exempts from regulation any establishment that removes human cells, tissues, and cellular and tissue-based products ("HCT/Ps") "from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b).

The SSP exception applies here, where Appellees remove cells from a patient, and then reimplant the *same* cells—which are not altered biologically—back into the same patient in the same procedure. The government's focus on manipulation is entirely misplaced. Whether Appellees manipulate the cells matters not one whit. While *other* regulations adopted by the FDA turn on the extent to which an HCT/P is manipulated, the SSP exception does not. The Court should reject the government's attempt to rewrite the SSP exception through litigation and should affirm the district court's judgment.

JURISDICTIONAL STATEMENT

Appellees agree with the government's jurisdictional statement.

ISSUES PRESENTED

1. Does the term "drug" in the FDCA provide the FDA with clear congressional authorization to regulate a surgical procedure performed by

licensed physicians that uses a patient's own cells and tissues to treat disease, and thereby interfere with the practice of medicine, which falls within the states' traditional police powers?

2. Does the regulatory exemption for establishments that remove a patient's tissues or cells and implant such tissues or cells into the same patient during the same surgical procedure apply when Appellees remove a patient's tissue that naturally contains stem cells, isolate such stem cells, and then implant those same stem cells into the same patient in the same surgical procedure?

STATEMENT OF THE CASE

A. Factual Background.

1. Dr. Mark Berman, Dr. Elliott Lander, Cell Surgical Network, and California Stem Cell Treatment Center.

Dr. Mark Berman was a physician licensed to practice medicine in the State of California since 1983.[1] 7-ER-925. Dr. Berman was board certified in head and neck surgery, as well as cosmetic surgery, and a fellow of the American College of Surgeons. 7-ER-927-928. Dr. Berman operated a surgical center in Beverly Hills, which was and is routinely inspected and

[1] Dr. Berman passed away on April 19, 2022. *See* Dkt. 11.

accredited in conformance with California law. 7-ER-930-932.

Dr. Elliot Lander is also a California-licensed physician, with board certification in urology, and a fellow of the American College of Surgeons. 8-ER-1257-1258. Dr. Lander operates a private practice in Rancho Mirage, and for nine years was President Ford's personal physician. 8-ER-1257.

Beginning in 1985, Dr. Berman pioneered a cosmetic procedure called "fat grafting," which involves removing fat—also known as "adipose" tissue—through liposuction and reinserting that fat into the same patient's face for a rejuvenated appearance. 7-ER-934-935. Through his experience working with adipose tissue, Dr. Berman began investigating the role of stem cells in adipose tissue and their potential uses for his patients. 7-ER-937-944.

Initially, Dr. Berman worked with an orthopedic surgeon who used the stem cells Dr. Berman derived from adipose tissue for orthopedic regeneration in the same patient. 7-ER-939, 942. Based on the successful results, in 2010, Dr. Lander expressed interest in harnessing the natural healing capabilities of a person's own stem cells to mitigate disease and degeneration. 8-ER-1263-1264. Together, Drs. Berman and Lander formed California Stem Cell Treatment Center and Cell Surgical Network, for the

purpose of treating patients with their own stem cells. 10-ER-1377.

2. Stem Cells Derived from a Patient's Adipose Tissue Heal Damage Within the Patient's Body.

Cells are the smallest and most basic functional structural units in the human body. 1-SER-154 ¶ 3. Every organ and tissue in the human body is composed of cells. 1-SER-268 ¶ 7. At its most basic level, a "stem cell" is an unspecialized cell that can develop into a specialized cell. *Stem Cell*, WEBSTER'S II NEW COLLEGE DICTIONARY 1106 (3d ed. 2005); *see also Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 924 n.1 (D.C. Cir. 2013) ("Stem cells are a cellular 'blank slate' that can change into a variety of other kinds of cells and generate additional stem cells. Those cells can be used to regenerate and repair damaged tissue.").

The stem cells at issue are "mesenchymal" stem cells, and naturally occur in adipose tissue. 8-ER-1159. Mesenchymal stem cells are "nurse cells," as they are "able to correct and repair and respond to … diseases and the like" in tissue. *Id.* When a physician injects stem cells into a damaged part of the body, the body's "environment" triggers mesenchymal stem cells to repair and correct damage "so that the tissue can get back to normal." 8-ER-1164-1165; *see also* 8-ER-1253 (stem cells

"have a complex signaling system that they use to find damage and hone in on it, and then send signals and in some cases actually replace damaged or dying cells to engraft and become new cells").

3. California Stem Cell's Stromal Vascular Fraction Surgical Procedure Removes, Isolates, and Reimplants a Patient's Stem Cells in the Same Surgical Procedure.

Since 2010, Drs. Berman and Lander have safely performed thousands of "stromal vascular fraction" or "SVF" Surgical Procedures involving their patients' own stem cells. 7-ER-1014-1015. SVF is a "simple surgical technique" that is performed as a single outpatient procedure. 7-ER-972; 1-ER-6 ¶ 7.

During the SVF Surgical Procedure, a licensed physician collects the patient's stem cells through a mini-liposuction technique. 1-ER-7-8. Using local anesthesia, the physician removes fifty milliliters of adipose tissue from the patient, and then places the mixture in a centrifuge to remove the anesthesia. 7-ER-972-974; 1-ER-7-8. Next, the physician uses FDA-cleared surgical devices and instruments and a medical-grade collagenase (an enzyme that breaks down collagen in tissue) developed by Roche to isolate the stromal vascular cells from the surrounding adipose tissue. 1-ER-7-8; 7-ER-1047. Once isolated from the adipose tissue, the cells are "freely

mobile" and thus bioavailable. 8-ER-1291. The solution is then "washed" three times with saline to remove the collagenase and centrifuged to isolate the SVF cells. 7-ER-978. Thereafter, the SVF cells are suspended in a sterile saline solution and relocated back into the patient's body. 1-ER-7-8.

As the district court found, a patient's cells are not altered in any way during the procedure, and the procedure "does not create any new material or introduce any foreign body into the body." 1-ER-8; *see also* 8-ER-1154, 1174-1175. The procedure neither changes the size, genetic makeup, or biological characteristics of the cells, nor affects their ability to proliferate. 1-ER-8. Rather, the same cells that naturally occur in the extracted adipose tissue are reimplanted into the "same patient during the same procedure." 1-ER-6.

The regenerative effects of California Stem Cell's SVF Surgical Procedure have been documented in peer-reviewed literature. For example, California Stem Cell performed the SVF Surgical Procedure on approximately 2,580 patients suffering from knee osteoarthritis, a degenerative form of arthritis. 8-ER-1299. Approximately 82% of the patients avoided surgery with sustained results of greater mobility and less pain, and the study demonstrated both good safety and efficacy. *See id.*;

Mark Berman, et al., *Prospective Study of Autologous Adipose Derived Stromal Vascular Fraction Containing Stem Cells for the Treatment of Knee Osteoarthritis*, INT'L J. OF STEM CELL RSCH. & THERAPY, Nov. 29, 2019 at 1, 9.

In another peer-reviewed publication, Dr. Lander utilized the SVF Surgical Procedure on approximately 109 patients with interstitial cystitis, a chronic condition that causes unremittent severe pelvic pain that patients describe as "the worst urine infection of their lives." 8-ER-1270-1271. Medications and other surgeries have been largely ineffective in treating interstitial cystitis. 8-ER-1270. But with the SVF Surgical Procedure, over 71% of patients reported that their pain had decreased, with no serious adverse events one year later. *See* Elliot B. Lander, et al., *Personal Cell Therapy for Interstitial Cystitis with Autologous Stromal Vascular Fraction Stem Cells*, THERAPEUTIC ADVANCES IN UROLOGY, Aug. 17, 2019, at 1, 2.

4. California Stem Cell's Expanded MSC Surgical Procedure Provides a Method for Treating Patients with Chronic Disease Who Are Unwilling or Unable to Undergo Multiple Surgeries.

For patients who are only able to undergo a single mini-liposuction procedure, California Stem Cell can perform an "expanded" procedure that involves sending the extracted adipose tissue to an FDA registered and inspected Current Good Manufacturing Practice ("cGMP") compliant

tissue bank to isolate mesenchymal stem cells for self-replication. 1-ER-8-9. Replication is a natural property of stem cells, and the replicated cells "retain all of the biological characteristics" of the original cells. 1-ER-9. Thus, the expanded cells "retain their cell markers, and do not differentiate while in the culture or during storage." *Id.* When the patient's cells are needed, the cGMP-compliant bank sends the stem cells in a sterile vial with the patient's information to Drs. Berman or Lander who deploy the cells back into the original patient. 1-ER-9 ¶ 23.

B. Statutory & Regulatory Background.

Appellees are subject to robust California statutory and regulatory schemes governing the licensing of physicians, the practice of medicine (including performance of surgery), and the licensing of healthcare facilities. Nonetheless, the FDA seeks to further regulate as "drugs" a physician's use of a patient's own tissues and cells to treat disease. And, notwithstanding the FDA's regulations, which expressly exclude "same surgical procedures" from the FDCA's reach (21 C.F.R. § 1271.15), the government argues Appellees must comply with the manufacturing and labelling standards that apply to the production of mass-produced pharmaceuticals.

1. The States Have Primary Authority to License, Regulate, and Discipline Physicians.

Over the last two centuries, the Supreme Court has repeatedly recognized the authority of the states to license, regulate, and discipline physicians. *See, e.g.*, *Gibbons v. Ogden*, 22 U.S. 1, 205 (1824) (noting that health laws "are considered as flowing from the acknowledged power of a State, to provide for the health of its citizens"); *Dent v. West Virginia*, 129 U.S. 114, 128 (1889) (holding that it was the province of the state to determine licensing requirements for physicians); *Hawker v. New York*, 170 U.S. 189, 193-94 (1898) ("Care for the public health is something confessedly belonging to the domain of [the State's] power.").

California, like other states, "has long regulated the practice of medicine as an exercise of the police power." *Arnett v. Dal Cielo*, 14 Cal. 4th 4, 7 (1996). For example, the Medical Board of California, a statewide agency, licenses and disciplines medical practitioners and has a statutory obligation to "protect the public against incompetent, impaired, or negligent physicians." *Id.* It may investigate unprofessional conduct (with corresponding subpoena powers), order licensees to submit to examination, and institute formal disciplinary action through the Attorney

General. *Id.* at 7-9.

Appellees, who are California physicians, must comply with stringent requirements, including the accreditation standards imposed on outpatient surgery centers. *See* 1-ER-8. Among other things, these accreditation standards require Appellees to maintain systems for patient care and monitoring, quality assessment and improvement, and subject themselves to peer review. *See* Cal. Health & Safety Code § 1248.15; 7-ER-932-933. And, of course, these standards of care co-exist with a medical malpractice regime that applies *ex post* in the case of a harmful surgical procedure. *See* Myrisha S. Lewis, *Halted Innovation: The Expansion of Federal Jurisdiction over Medicine and the Human Body*, 2018 UTAH L. REV. 1073, 1091 (2018).

2. The FDA Historically Has Not Regulated Surgical Procedures Involving Human Tissues and Cells.

Before 1997, the FDA—which has existed since 1906—exerted little or no regulatory control over human cells and tissues. Nonetheless, the FDA now claims authority to regulate as "drugs" a patient's own cells and tissues used to treat or mitigate disease.

a. The Food, Drug & Cosmetic Act of 1938.

The FDCA has its origins in the Pure Food and Drug Act of 1906 ("PFDA"), which was passed to alleviate concerns about food contamination. Mary Ann Chirba & Stephanie M. Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine?*, 7 J. HEALTH & BIOMEDICAL L. 233, 241 (2011). While focused on food, the PFDA included limited oversight of drugs. It required manufacturers to monitor their drugs for strength, quality, and purity, but failed to enumerate standards or specific methods of pre-market testing to prevent adulteration. *See* Pure Food and Drug Act of 1906, Pub. L. No. 59-384, c. 3915, 34 Stat. 768, 768 (1906) (repealed 1938).

In the wake of a mass poisoning from the use of an antimicrobial drug, Congress enacted the FDCA and authorized the FDA to regulate "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded." Food, Drug, and Cosmetic Act of 1938 § 301(a), Pub. L. No. 75-717, c. 3915, 52 Stat. 1040, 1042 (1938); *see* Roseann B. Termini & Anthony Knabb diDonato, *The Role and Mission of the United States Food and Drug*

Administration, 7 BIOTECHNOLOGY & PHARM. L. REV. 901, 905-06 (2014).

The FDCA defined the term "drug" to include four categories of articles: (1) "articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them;" (2) "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"; (3) "articles (other than food) intended to affect the structure of any function of the body of man or other animals"; and (4) "articles intended for use as a component of any article" specified in the first three clauses. Food, Drug, and Cosmetic Act § 201(g).

Under the FDCA, a "drug" is "adulterated" if, among other things, the facilities or controls used for its manufacture do not conform to cGMP standards. 21 U.S.C. § 351(a)(1)(B). The FDA's cGMP regulations establish standards for drug manufacturing facilities, personnel, and sanitation. *See, e.g.*, 21 C.F.R. § 211.42 (facilities), § 211.22 (quality control unit), § 211.28 (personnel responsibilities), and §§ 211.48-211.50 (sanitation). For example, drug manufacturers must: mark each piece of major equipment with an identification number of code that shall be recorded in the "batch

production record" of each batch of a drug product (21 C.F.R. § 211.105); calculate actual yields and percentages of theoretical yield at the conclusion of each manufacturing phase (*id.* § 211.103); conduct samples of in-process materials of every drug batch to ensure uniformity (*id.* § 211.110); and establish a written testing program that determines appropriate expiration dates (*id.* § 211.166).

Under the FDCA, a "drug" is "mislabeled" unless it includes a label with the drug's established name, quantity, and proportion of active and inactive ingredients. 21 U.S.C. § 352(e)(1)(A). In addition, the drug must be labeled with "adequate directions for use." *Id.* § 352(f). Adequate directions include, *inter alia*, the dosage, frequency, and duration of administration, time of administration in relation to time of meals, and route or method of administration. 21 C.F.R. § 201.5.

b. The FDA's HCT/P Regulations.

In 1997, the FDA proposed in a guidance document to expand its authority to reach human cells, tissues, cellular- and tissue-based products, or "HCT/Ps." FDA, *Proposed Approach to Regulation of Cellular and Tissue-Based Products* (Feb. 28, 1997) ("1997 Proposed Approach"). HCT/Ps are "articles containing or consisting of human cells or tissues that are

intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).

The FDA followed its 1997 guidance statement with a proposed regulation. *See Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products*, 63 Fed. Reg. 26744 (May 14, 1998). The FDA's purported authority to issue regulations governing human cells and tissues flowed not from the FDCA, but from the Public Health Service Act ("PHSA"), which authorizes the FDA "to make and enforce such regulations as … are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." 42 U.S.C. § 264(a); *see Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing*, 66 Fed. Reg. 5447, 5548 (Jan. 19, 2001) (to be codified at 21 C.F.R. § 1271).[2] Under this

[2] The PHSA also authorizes the FDA to regulate "biologic products." 42 U.S.C. § 262(i)(1), which are defined as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." The government summarily asserts on appeal that human cells and tissues are subject to regulation as "biological product[s]" under

authority, the FDA announced its intention to regulate cells and tissues under a "tiered" approach, depending on the safety risk of the regulated product. 63 Fed. Reg. at 26745.

1. No oversight. The FDA exempted from regulation "[a]n establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b). As the FDA explained, "autologous" use of cells—that is, cells from the *same* individual—transplanted in a single surgical procedure are "subject to no FDA oversight" because "[t]he communicable disease risks, as well as the safety and effectiveness risks, would generally be no different than those typically associated with surgery." 1997 Proposed Approach at 12, 15.

In 2017, the FDA finalized new guidance, interpreting the SSP exception to require that the patient's transplanted HCT/P be implanted in

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the PHSA. AOB 5. But as in the district court, the government never explains to *what* biologic a patient's stem cells are analogous. By failing to provide such foundation, the government has forfeited any reliance on the PHSA as a jurisdictional basis for regulating a patient's stem cells as biologic products, and Appellees will not address the reach of that statute here. *Orr v. Plumb*, 884 F.3d 923, 932 (9th Cir. 2018).

its "original form." FDA, *Same Surgical Procedure Exception Under 21 CFR 1271.15(b)* at 5 (Nov. 2017) ("2017 Guidance"). "Generally," the FDA asserts, "the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleansing, sizing, and shaping." *Id.*

2. Limited Oversight. If a product does not fall under the SSP exception, it is subject to limited oversight if it meets the four criteria of 21 C.F.R. § 1271.10. HCT/Ps that qualify under § 1271.10 are regulated under section 361 of the PHSA and 21 C.F.R. § 1271, but not under the FDCA. FDA, *Regulatory Considerations for Human Cells, Tissues and Cellular and Tissue-Based Products* at 6 (July 2020) ("2020 Guidance"). To qualify for this limited regulatory oversight, the HCT/P must, among other things, be "minimally manipulated." 21 C.F.R. § 1271.10(a)(1)-(2).

3. More expansive oversight. Finally, if a product meets the definition of HCT/P, but neither the SSP exception nor the four 21 C.F.R. § 1271.10(a) criterion apply, the HCT/P may be regulated under the FDCA, PHSA, and any applicable regulations.

C. Procedural Background.

1. The FDA filed suit against California Stem Cell, Cell Surgical Network, and Drs. Berman and Lander in the Central District of California

on May 9, 2018. 2-ER-67. The FDA alleged that the stem cells Appellees derive from adipose tissue are "drugs" under the FDCA because they are intended to mitigate or treat disease, and because they are intended to affect the structure or function of the body. 2-ER-73 (citing 21 U.S.C. § 321(g)(1)(B)-(C)).

The FDA alleged that the cells Appellees derive from patients are adulterated in violation of the FDCA because they are not manufactured in conformity with current good manufacturing practice. 2-ER-78 ¶ 47. The FDA further alleged the cells are misbranded because the cells and their labeling failed to bear adequate usage directions. 2-ER-80 ¶ 52. The government therefore sought to permanently enjoin Appellees from "doing any act" with respect to a patient's cells that results in adulteration or misbranding under the FDCA. 2-ER-83-84.

2. The government moved for summary judgment on its claim that Appellees' procedures violate the FDCA, which the district court denied. 1-ER-31. The district court held that there was a triable issue of fact whether Appellees' SVF Surgical Procedure is exempt from FDA oversight under the SSP exception. 1-ER-34.

Specifically, the court held that the phrase "such HCT/Ps" is

unambiguous; it "requires that the implanted HCT/P's" be "the same HCT/P's as those that were removed." 1-ER-31. Thus, if a physician removes an HCT/P from Patient One and implants it in Patient Two—*i.e.*, an allogeneic transfer—"the exception clearly does not apply." *Id.* Likewise, if a doctor "removes an HCT/P, mutates it then implants it back into the patient," the exception would not apply because "the implanted HCT/P is not 'such HCT/P' as was removed." *Id.*

In so holding, the district court rejected the government's argument that the SSP exception is inapplicable whenever a physician implants cells excised or derived from extracted tissue. 1-ER-31-32. The court explained that the term "HCT/P" is an acronym for "[h]uman cells, tissues, or cellular or tissue based products." 1-ER-31. Because cells make up tissues and organs, "cells can only be removed from a patient along with those larger systems." 1-ER-32. Thus, if the SSP exception "demanded the removal to be characterized by the largest system that was removed," then it would never apply to the removal and implantation of a cell, thereby rendering "cells" and "cellular … based products" superfluous. *Id.*

Moreover, the court observed, the term HCT/P is defined by reference to those cells or tissues "that are intended for implantation,

transplantation, infusion, or transfer into a human recipient." 1-ER-31 (quoting 21 C.F.R. § 1271(d)). Because the term is defined by HCT/Ps *intended* for implantation, it makes more sense to define HCT/Ps based on the target of the removal, rather than the largest system removed. 1-ER-33. And because "most if not all surgical removals take out more biological matter than what was targeted," it would be unreasonable to require that a surgeon implant everything that was removed—including excess blood or tissue matter never intended to be reimplanted—for the exception to apply. *Id.*

Accordingly, the court held that the SSP exception applies if cells are removed and then reimplanted into the same patient without alteration of the cells themselves. This is true "even when they [are] removed along with other biological material … not ultimately [re]implanted." 1-ER-34. Because it was disputed whether the SVF Surgical Procedure "alters the SVF cells," the court denied summary judgment to the government. *Id.*

3. The district court subsequently held a seven-day bench trial, during which the government and Appellees presented various witnesses and experts. On August 30, 2022, the district court issued findings of fact and conclusions of law and entered judgment in favor of Appellees. 1-ER-

3-21.

The district court held that neither the SVF Surgical Procedure nor the Expanded MSC Surgical Procedure are "drugs" within the meaning of the FDCA, and thus are not subject to its adulteration and misbranding provisions. 1-ER-13. The Court first noted that the FDA does not regulate surgery, even though it often involves dissecting, isolating, and relocating tissues and cells to treat disease in the human body. 1-ER-6. Noting that the line between FDA-regulated "drugs" and state-regulated surgical "procedures" is muddy, particularly "when licensed medical doctors enter a patient's body, extract that patient's cells, and reintroduce those cells to that patient after some amount of cellular processing," the court concluded that the SVF Surgical Procedure and Expanded MSC Surgical Procedure constitute the practice of medicine, and not something the FDCA has jurisdiction to regulate. 1-ER-13, 16, 18-19. With respect to the Expanded MSC Surgical procedure, in particular, the court explained that the cells involved "are not fungible goods that can be sold, mass produced, or patented," but are "human cells removed from patients and then reintroduced into those same patients." 1-ER-18.

The court further held that the SVF Surgical Procedure is exempt

from regulation under the SSP exception. 1-ER-14-15. On the question that it reserved at summary judgment, the court found that "[t]he SVF Cells are not altered, chemically or biologically, at any point during the SVF Surgical Procedure." 1-ER-8; *see also* 1-ER-16-17. Because the SVF Surgical Procedure involves reinjecting unaltered SVF cells, or "such cells," into the patient during the same surgical procedure, it is within the SSP exception. 1-ER-15.

STANDARD OF REVIEW

Following a bench trial, the district court's findings of fact are reviewed for clear error and its conclusions of law are reviewed *de novo*. *See Oakland Bulk & Oversized Terminal, LLC v. City of Oakland*, 960 F.3d 603, 612 (9th Cir. 2020). The district court's findings of fact must be accepted unless the reviewing court is left with a definite and firm conviction that a mistake has been made. *See Kohler v. Presidio Int'l, Inc.*, 782 F.3d 1064, 1068 (9th Cir. 2015). This Court "may affirm a district court's judgment on any ground supported by the record, whether or not the decision of the district court relied on the same grounds or reasoning we adopt." *Atel Fin. Corp. v. Quaker Coal Co.*, 321 F.3d 924, 926 (9th Cir. 2003).

SUMMARY OF THE ARGUMENT

Based on the evidence presented at trial, the district court held that Appellees' SVF Surgical Procedure and Expanded MSC Surgical Procedure are not "drugs," and that the SVF Surgical Procedure is exempt from regulation under the SSP exception. The district court was correct in both respects.

1. The government argues that a patient's stem cells are "drugs" under the FDCA because a physician mobilizes them to treat or mitigate disease. But under the government's mechanical interpretation, every time a physician uses a patient's own cells to treat or mitigate disease, she manufactures a drug. This interpretation proves too much: it cannot be that Congress intended to impose drug manufacturing and labeling guidelines on every physician who performs a hair transplant, bone graft, fat graft, or venous bypass surgery.

Nor has the Supreme Court permitted such expansive agency jurisdiction. As the Court recently explained, a colorable textual basis for agency jurisdiction is not enough. Statutes conferring authority on an administrative agency must be read in their context and shaped by the question whether Congress meant to confer the power asserted. Here, the

FDCA's legislative history contradicts the government's assertion that Congress intended to delegate the FDA jurisdiction over surgical procedures and the physician-patient relationship, which historically has fallen within the states' traditional police powers.

Because the FDA seeks to intrude into an area that is the particular domain of state law, the FDA must point to clear congressional authorization. It cannot do so. Congress' vague statutory grant of authority over "drugs" does not approximate the clear authorization required by Supreme Court precedent.

2. Even if the FDA had a colorable argument for jurisdiction over Appellees' surgical procedures, the SVF Surgical Procedure is exempt from regulation under 21 C.F.R. § 1271.15(b), which applies when an "establishment … removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure."

The SSP exception applies here because Appellees (a) remove HCT/Ps (human cells) from an individual; (b) implant the same biologically unaltered HCT/Ps; (c) into the same individual; (d) during the same surgical procedure. 1-ER-14-15. To avoid this straightforward interpretation, the government improperly attempts to rewrite the SSP

exception, arguing it applies only when the article removed remains in its original form. The government's proposed construction is manufactured out of whole cloth and defies both common sense and basic interpretive principles.

Nothing in § 1271.15(b)'s plain text limits the exception to circumstances where the physician reimplants the largest system removed. Rather, the SSP exception requires only that the reimplanted tissues or cells be the same tissues or cells removed: nothing more, nothing less.

Moreover, the government's interpretation makes little practical sense. Virtually all surgeries remove more biological matter than is reimplanted or transposed. And cells can only be removed from a patient along with larger systems, such as the tissues they comprise. If the government were correct, then the SSP exception would never apply to cells, thereby rendering superfluous the very definition of HCT/Ps—which includes both "cells" and "cellular-based products."

Contrary to the government's sky-is-falling rhetoric, the district court's interpretation of the SSP exception does not permit "nearly limitless manipulation and recombination of cells and tissues." AOB 19. For the SSP exception to apply, the cells that a physician removes must still be, as

the district court held, the *same* cells as those removed. So, a manufacturing process that altered a patient's cells biologically would not qualify. Here, however, the district court found that the SVF Surgical Procedure does not alter a patient's cells, a finding the government does not contest, and which is amply supported by the trial record.

Ultimately, the government retreats to a plea for deference. But deference is not warranted under *Kisor v. Wilkie*'s three requirements. 139 S. Ct. 2400 (2019). The SSP exception is unambiguous. The government's interpretation is unreasonable. And the guidance policy on which the government relies for its interpretation does not make authoritative policy. The district court's judgment should be affirmed.

ARGUMENT

I. CONGRESS DID NOT AUTHORIZE THE FDA TO REGULATE A PHYSICIAN'S USE OF AUTOLOGOUS STEM CELLS TO TREAT DISEASE AS "DRUGS" UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

The district court correctly held that in authorizing the FDA to regulate "drugs," Congress did not intend to empower the FDA to regulate surgery.

A. The Government's Strained and Overbroad Interpretation of "Drugs" Produces a Sequence of Irrational Results.

Before delving into the question presented, it is worth pausing for a moment to consider the practical implications of the government's position. This is critical, because when a superficial examination of a Congressional grant of authority would lead to absurd results, or even an unreasonable one at variance with the policy of the legislation as a whole, the statute's "purpose" must take precedence over "the literal words." *United States v. Am. Trucking Ass'ns*, 310 U.S. 534, 543 (1940).

The FDCA's definition of "drugs" is admittedly capacious. But the government's position pushes its jurisdiction beyond the bounds of reason. Consider the many surgical procedures that use a patient's own body parts to treat, cure, or mitigate disease. For example, approximately 200,000 patients in the United States receive heart bypass surgery every year. Ludovic Melly, et al., *Fifty Years of Coronary Artery Bypass Grafting*, 10 J. OF THORACIC DISEASE 1960, 1960 (2018). It is standard in bypass surgeries for a physician to take a vein or artery from one part of the patient's body (like the leg) and use it to make a detour around a blockage in the heart to create a new route for blood and oxygen. *Id.* Under the government's

interpretation of the FDCA, a surgeon performing a bypass surgery creates a "drug" by using a leg vein to "affect the structure of the [patient's] body." The vein similarly can be said to "mitigate," "treat" and "prevent" heart disease. *See* 21 U.S.C. § 321(g).

Something as mundane as a hair transplant would also fall within the purview of the FDA's proposed interpretation of "drugs." Androgenic alopecia—male pattern baldness—is a common genetic disorder. The FDA has approved two drugs to treat the condition (minoxidil by Johnson & Johnson, and finasteride by Merck). *See* Mark S. Nestor, *Treatment Options for Androgenetic Alopecia*, 20 J. COSM. DERMATOLOGY 3759, 3760 (2021). But another common treatment is hair transplant surgery, which involves surgically excising and transferring follicles of healthy hair and moving the graft to the hairless part of the patient's scalp. *See* Manoj Khanna, *Hair Transplantation Surgery*, INDIAN J. PLAST SURG., Oct. 2008. Under the FDA's theory, a patient's own hair and scalp is no less a "drug" than the oral and topical medications it has approved for hair loss.

It is at the very least unreasonable to assert that Congress intended for a plastic surgeon conducting hair transplant surgery to be subjected to the same regulatory regime as pharmaceutical companies. This illogic is

only compounded when the adulteration and misbranding standards applicable through the FDCA and FDA regulations are applied to a physician's operating room. "The FDA requirements, designed for products manufactured and sold on a mass scale, can't be readily satisfied when it comes to treatments that are personalized to individual patients." Scott Gottlieb & Coleen Klasmeier, *The FDA Wants to Regulate Your Cells*, WALL STREET J. (Aug. 7, 2012).

For example, under the government's reading, physicians who use autologous tissues or cells to treat disease must label those tissues and cells with information about the dose, frequency, and route of administration. Is the plastic surgeon performing hair transplant surgery supposed to halt the proceedings so she can label the patient's hair follicles before reattachment?

And if cGMP regulations were applied to autologous cells and tissues, operating rooms would require the same quality assurance program as a sterile manufacturing facility. As a result, the physician would be required to test an "adequate number" of her patient's tissues and cells to determine an appropriate expiration date for those body parts. 21 C.F.R. § 211.116(b). Before completing the surgery, the physician must

swab the patient's tissue or cells to test for microbial contamination. *Id.* § 211.165(b). And after completing each surgery, the physician must prepare a log that includes the name and strength of the patient's tissue or cells, its active ingredients and weight, and a statement of "theoretical yield," whatever that might mean in this context. *Id.* § 211.186. Not to mention each physician's office with operating room would have to comply with the lighting, ventilation, plumbing, sewage, toilet, and sanitation standards that apply to sterile pharmaceutical manufacturing factories. *Id.* § 211.42-211.58.

While the FDA has sought to alleviate some of these consequences by excepting, on the back end, certain common surgeries from the full force of its cGMP regulations—by, for example, assuring physicians that it does not intend to regulate autologous skin grafting and venous bypass surgery (AOB 7)—that does not speak to whether Congress intended for the FDA to exercise this expansive jurisdiction under the FDCA. If anything, the FDA's transparent parsing between those surgeries it deems worthy and those it seeks to regulate out of existence begs the question: by giving the FDA jurisdiction over "drugs," did Congress intend to bestow authority on the FDA to regulate surgeries? As Appellees will now explain, a proper

textual analysis of the FDCA confirms that Congress did not so intend.

B. Pursuant to the Major Questions Doctrine, the Meaning of "Drugs" Must Be Ascertained in Light of Common Sense and Congressional Intent.

The crux of the government's position is that a plain reading of the FDCA compels the conclusion that a patient's stem cell is a drug. Stem cells are "article[s]" used by Appellees to mitigate or treat disease, and thus satisfy the definition of "drugs." 21 U.S.C. § 321(g)(1).

The D.C. Circuit adopted this mechanical and context-avoidant reading of "drug" in *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014), concluding "that the plain language of the [FDCA] compels this conclusion."[3] Since 2014, however, the United States Supreme Court has clarified that where a statute "confers authority upon an administrative agency," the words used in that statutory grant must be read in context. The inquiry "must be 'shaped, at least in some measure, by the nature of the question presented'—whether Congress in fact meant

[3] Contrary to the government's assertion (AOB 21), the definition of "drug" as used in the FDCA was not disputed in *United States v. U.S. Stem Cell Clinic, LLC*, 998 F.3d 1302 (11th Cir. 2021). *See* Br. for Defs.-Appellants, *United States v. US Stem Cell Clinic, LLC*, 2019 WL 5692810 (11th Cir. Oct. 31, 2019).

to confer the power the agency has asserted." *West Virginia v. E.P.A.*, 142 S. Ct. 2587, 2607-08 (2022) (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 159 (2000)).

Attention to context is particularly important in "extraordinary cases" like this one—denominated "Major Question" cases—that require a different or "atextual" approach. In such cases, the "history and breadth of the authority that the agency has asserted," and "the economic and political significance" of that assertion, provide a "reason to hesitate before concluding that Congress" meant to confer such authority. *Id.* at 2608 (quotation marks and citation omitted). This is such a case.

1. The FDA Seeks to Intrude Into an Area that Is the Particular Domain of State Law.

Under the Major Questions Doctrine, an agency must point to clear congressional authorization when it seeks to regulate an area that is the particular domain of state law. *West Virginia*, 142 S. Ct. at 2587 (Gorsuch, J., concurring); *Ala. Ass'n of Realtors v. Dep't of Health & Hum. Servs.*, 141 S. Ct. 2485, 2489 (2021). To preserve the "proper balance between the States and the Federal Government," courts must "'be certain of Congress's intent'" before finding that it "legislate[d] in areas traditionally regulated by the

States." *Gregory v. Ashcroft*, 501 U.S. 452, 459-60 (1991).

Here, the FDA seeks to intrude on two areas traditionally regulated by the states: the practice of medicine and the patient-physician relationship. "Since colonial times, the regulation of professions," including the practice of medicine, "has been seen as a state activity in the United States." Edward P. Richards, *The Police Power & the Regulation of Medical Practice*, 8 ANNALS OF HEALTH L. 201, 202 (1999). Thus, state lawmakers, not the federal government, are "the primary regulators of professional [medical] conduct." *Conant v. Walters*, 309 F.3d 629, 639 (9th Cir. 2002). As the Supreme Court explained in *Gonzales v. Oregon*, 546 U.S. 243, 269-70 (2006), "the structure and limitations of federalism" allow the States "great latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons." Accordingly, the federal government "may not ... regulate [the doctor-patient] relationship to advance federal policy." *Oregon v. Ashcroft*, 368 F.3d 1118, 1124 (9th Cir. 2004) (quotation marks and citation omitted), *aff'd sub nom. Gonzales v. Oregon*, 546 U.S. 243 (2006).

Nonetheless, the government argues it is commonplace for the FDCA to prohibit certain acts involving drugs, "even when they involve a doctor

purporting to treat a patient." AOB 23 (citing 21 U.S.C. §§ 331, 351, 352). However, the FDA's power to regulate the practice of medicine is specific and limited and must be supported by "unmistakably clear" statutory language. *Judge Rotenberg Educ. Ctr., Inc. v. FDA*, 3 F.4th 390, 399 (D.C. Cir. 2021) (quoting *Will v. Mich. Dep't of State Police*, 491 U.S. 58, 65 (1989)). Here, by expanding the definition of "drugs" to encompass the extraction and reimplantation of a patient's autologous stem cells, the FDA is interfering with both patients' right to control their bodies and their physician's right to "[c]hoos[e] what treatments are or are not appropriate for a particular condition," which "is at the heart of the practice of medicine." *Id.* at 400. Accordingly, clear congressional authorization is required.

The FDA's intrusion into the physician's operating room not only upsets the federal-state balance, it also intrudes on the rights of patients. "Federalism is more than an exercise in setting the boundary between different institutions of government for their own integrity." *Bond v. United States*, 564 U.S. 211, 221 (2011). Federalism also protects the "liberty of all persons within a State by ensuring that laws enacted in excess of delegated governmental power cannot direct or control their actions." *Id.* at 222. In

other words, federalism concerns individual freedom. *See id.*; *New York v. United States*, 505 U.S. 144, 181 (1992) ("[F]ederalism secures to citizens the liberties that derive from the diffusion of sovereign power.").

By delegating police powers to fifty different states, instead of one national sovereign, the Framers ensured that "the facets of governing that touch on citizens' daily lives are normally administered by smaller governments closer to the governed." *Nat'l Fed'n of Indep. Bus. v. Sebelius*, 567 U.S. 519, 536 (2012). Patients benefit from state control over health care practices, "whether they wish to influence elected officials' decisions about the availability of controversial medical procedures or, if unsuccessful in lobbying for access, to seek out care in more accommodating adjacent states." Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 187 (2004). Therefore, when a federal agency like the FDA claims jurisdiction over forums typically regulated under the states' police powers, not only are principles of federalism and separation of powers at risk, but so are individual liberties. *See Cruzan by Cruzan v. Dir., Mo. Dep't of Health*, 497 U.S. 261, 269 (1990) ("Every human being of adult years and sound mind has a right to determine what shall be done with his own body.") (quotation marks and

citation omitted).

In short, by regulating a physician's use of a patient's own body for surgical purposes, the FDA's interpretation of "drugs" "interferes with [California's] authority to regulate medical care within its borders and therefore alters the usual constitutional balance between the States and the Federal Government." *Ashcroft*, 368 F.3d at 1124. As a result, Congress' jurisdictional grant must be "unmistakably clear" before the FDA can exercise control over Appellees' surgical use of their patient's autologous stem cells. *Id.* at 1125.

2. The FDCA's Legislative History, Which Expresses the Intent Not to Interfere with the Practice of Medicine, Requires Clear Congressional Authorization to Regulate the Autologous Use of a Patient's Body Parts.

The FDCA's legislative history clearly evinces Congress's intent to avoid interfering with the practice of medicine. In light of that history, the government must identify unmistakably clear language before regulating a physician's use of a patient's autologous stem cells to treat disease. *West Virginia*, 142 S. Ct. at 2609.

The FDA itself has recognized that in debates leading up to the enactment of the FDCA and its amendments, "there were repeated

statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient." *Legal Status of Approved Labeling for Prescription Drugs*, 37 Fed. Reg. 16503, 16503 (Aug. 15, 1972). That is why, in 1972, the FDA determined that if a drug has been approved for one use, physicians may use that drug at a different dose or for a different purpose without federal interference. *Id.* at 16504; *see also New Drug, Antibiotic, and Biologic Drug Product Regulations*, 52 Fed. Reg. 8798, 8803 (Mar. 19, 1987) ("[I]t was clearly the intent of Congress in passing the Federal Food, Drug, and Cosmetic Act that FDA not regulate the practice of medicine"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 n.5 (2001) (while the FDCA prevents manufacturers from promoting off-label use of drugs, it does not prevent physicians from prescribing or using FDA approved drugs in a manner inconsistent with the FDA-approved labeling because to do so would interfere with the state-regulated practice of medicine).

The legislative history of the FDCA confirms that Congress "was determined to preclude FDA interference with the medical profession."

Chirba, 7 J. HEALTH & BIOMEDICAL L. at 242. The statute's primary author, former physician Senator Royal Copeland, responded to fears that the proposed legislation would interfere with the "prerogatives of the doctor" by emphasizing that the revised bill "makes certain that the medical practitioner shall not be interfered with in his practice." *See* 78 Cong. Rec. 2728 (1934) (statement of Sen. Copeland).

Signifying that there may be some overlap between the definition of "drug" and the practice of medicine, the definition of "drug" originally contained language stating that it was not intended "for the regulation of the legalized practice of the healing art." 4 FDA, *A Legislative History of the Federal Food, Drug, and Cosmetic Act and Its Amendments* 180 (1979). The language was to clarify that the bill was "not a medical practices act" and was not meant to "interfere with the practice of the healing art by chiropractors and others in the States where they are licensed by law to engage in such practice." 3 *A Legislative History of the Federal Food, Drug, and Cosmetic Act and Its Amendments* at 662. The American Medical Association, however, feared that by including this language, Congress would unintentionally imply that non-drug provisions in the Act *did* regulate the practice of medicine. 4 *A Legislative History of the Federal Food,*

Drug, and Cosmetic Act and Its Amendments at 610-13. Accordingly, the Association recommended that Congress either delete the phrase, or adopt a different provision stating that nothing in the FDCA should be construed as limiting the right of physicians to use or prescribe for the treatment of disease "anything that he is authorized by his license or registration to employ for that purpose." *Id.* at 613.

In the end, Congress deleted the proviso making clear that the term "drugs" was not intended to regulate the medical practice. According to the Committee that submitted the report to Congress on the final version of the bill, the deletion was made "to avoid possible misunderstanding," and because the words were unnecessary as "***[t]he bill does not undertake to regulate the practice of the healing art.***" 5 FDA, *A Legislative History of the Federal Food, Drug, and Cosmetic Act and Its Amendments* 148 (emphasis added); *see also* Chirba, 7 J. HEALTH & BIOMEDICAL L. at 242 (explaining how the proviso was rejected as superfluous).

Downplaying any interference with the practice of medicine, the government professes merely to be regulating an *article* (the stem cells themselves), not the *procedure* by which physicians inject that article into their patients. AOB 23; *see Regenerative Scis.*, 741 F.3d at 1318-19. That,

however, is mere semantics. The government is attempting to regulate *steps* of the surgical procedure. Indeed, the point of Appellees' procedure is to transpose a patient's own bodily components. This the very definition of surgery. *See* Am. Med. Ass'n, *Definition of Surgery H-475.983* (2013) ("Surgery … is the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or *transposition* of live human tissue.") (emphasis added). The legislative history makes clear that the FDCA should not interfere with the practice of medicine which, unquestionably, includes surgery. Accordingly, the FDA must point to unmistakably clear language before asserting jurisdiction over Appellees' surgical procedures.

C. The FDA Is Not Clearly Authorized to Regulate Appellees' Surgical Procedures.

Because both principles of federalism and the FDCA's legislative history are at odds with the FDA's interpretation, the FDA must point to "clear congressional authorization" that grants it authority over a physician's use of a patient's body parts to treat disease. *West Virginia*, 142 S. Ct. at 2614. In determining whether a grant of authority qualifies as a clear congressional statement authorizing an agency's action, Supreme

Court precedent has identified four "telling clues." *Id.* at 2622 (Gorsuch, J., concurring). All four of those clues weigh against the FDA's position.

1. The FDCA's Definition of Drugs Is Cryptic.

First, Congress does not "typically use oblique or elliptical language to empower an agency to make a 'radical or fundamental change' to a statutory scheme." *West Virginia*, 142 S. Ct. at 2609. Notably, the Supreme Court has *already* concluded that the statutory provision at issue here—the FDCA's definition of "drug"—is a "cryptic" grant of authority. *Brown & Williamson*, 529 U.S. at 160.

Relying on *United States v. An Article of Drug ... Bacto-Unidisk*, 394 U.S. 784, 793, 798 (1969), the government argues that "drug" is defined expansively and that "'Congress fully intended that the [FDCA's] coverage be as broad as its literal language indicates.'" AOB 17. Notwithstanding this dictum, "[a] careful reading of" *Bacto-Unidisk* "demonstrates that the Supreme Court was "responding to specific indications in the legislative history that Congress intended the premarketing approval requirements for drugs to apply as well to devices." *Am. Health Prods. Co. v. Hayes*, 574 F. Supp. 1498, 1502 (S.D.N.Y. 1983), *aff'd on other grounds*, 744 F.2d 912 (2d Cir. 1984). Such specific indications do not exist here. To the contrary, the

legislative history counsels against extending the FDA's jurisdiction to the practice of medicine.

In any event, the Supreme Court's subsequent opinion in *Brown & Williamson* confirms that *Bacto-Unidisk* cannot be read in a vacuum. In *Brown & Williamson*, the FDA claimed jurisdiction over tobacco as a "drug" because, under a plain reading of the term, tobacco is an article intended to affect the structure of any function of the body of man. *See* 529 U.S. at 162 (Breyer, J., dissenting) ("[T]obacco products (including cigarettes) fall within the scope of this statutory definition, read literally[.]"). The Supreme Court rejected that "expansive construction of the statute," concluding that "Congress could not have intended to delegate" such a sweeping and consequential authority "in so cryptic a fashion." *Id.* at 160. Under *Brown & Williamson*, the FDCA's definition of "drugs" is too cryptic to allow the FDA to authorize regulating a physician's use of a patient's stem cells to treat disease.

2. It Is Implausible Congress Intended to Regulate the Surgical Use of Autologous Stem Cells Through an Eighty-Five-Year-Old Definition.

Second, "courts may examine the age and focus of the statute the agency invokes in relation to the problem the agency seeks to address."

West Virginia, 142 S. Ct. at 2623 (Gorsuch, J., concurring). It is unlikely that Congress will make an "[e]xtraordinary gran[t] of regulatory authority" through "vague language" in "'a long-extant statute.'" *Id.* at 2609-10 (majority op.).

Recently, the Supreme Court held a "clear statement lacking when OSHA sought to impose a nationwide COVID-19 vaccine mandate based on a statutory provision that was adopted 40 years before the pandemic and that focused on conditions specific to the workplace rather than a problem faced by society at large." *Id.* at 2623. Similarly, "[a]t the time the [FDCA] was passed," stem cells and their benefits "were unknown." *Blank v. United States*, 400 F.2d 302, 303 (5th Cir. 1968).

While old statutes can be written in ways that apply to new and previously unanticipated situations, *Sedima, S. P. R. L. v. Imrex Co.*, 473 U.S. 479, 499 (1985), an agency's attempt to deploy an "old statute focused on one problem to solve a new and different problem may also be a warning sign that it is acting without clear congressional authority," *West Virginia*, 142 S. Ct. at 2623 (Gorsuch J., concurring).

That is the case here. Congress enacted the FDCA in 1938 to respond to the broad availability of falsely promoted and deadly drugs. *See* Karen

Baswell, *Time for A Change: Why the FDA Should Require Greater Disclosure of Differences of Opinion on the Safety and Efficacy of Approved Drugs*, 35 HOFSTRA L. REV. 1799, 1809 (2007) (FDCA passed after more than 100 people died from ingesting a poisonous elixir marketed as a "wonder drug"). The FDA's attempt to transform an 85-year-old statute focused on tainted, chemically-synthesized products to one governing a surgeon's use of a patient's own cells and tissues is strong evidence that the FDA is overstepping its jurisdictional bounds.

3. The FDA Claims to Have Found a Previously Unheralded Power.

Third, in examining whether a jurisdictional grant provides an agency with clear congressional authorization, "courts may examine the agency's past interpretations of the relevant statute." *West Virginia*, 142 S. Ct. at 2623 (Gorsuch, J., concurring). Whereas a contemporaneous and long-held agency interpretation of a statute is entitled to some weight as evidence of the statute's original charge, an agency's assertion warrants skepticism when it claims to have found a previously unheralded power. *Id.* (citing *Brown & Williamson*, 529 U.S. at 158-59; *Util. Air Regul. Grp. v. E.P.A.*, 573 U.S. 302, 324 (2014)).

Almost sixty years transpired between the enactment of the FDCA in 1938 and the FDA's 1997 announcement that it had "designed a new regulatory framework for cells and tissues." *Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting*, 62 Fed. Reg. 9721, 9721 (Mar. 4, 1997). The FDA acknowledged at the time that "[t]issues have long been transplanted in medicine for widespread uses." 1997 Proposed Approach at 6. Yet suddenly, the FDA claimed to have jurisdiction over such procedures, enabling it to "set boundaries between the kinds of experimentation with human products that warrant only minimal FDA oversight and the kinds of experimentation with human products that warrant greater FDA oversight." *Id.* at 27.

More fundamentally, the FDA has never claimed jurisdiction to regulate HCT/Ps under the FDCA; rather, the FDA asserted that its regulatory authority arose "solely under" the PHSA. 63 Fed. Reg. at 26747. And even then, the FDA stated that its regulations would "not apply to autologous human tissue." 21 C.F.R. § 1270.1(c) (2005).

Indeed, between 1997-2005, the FDA asserted jurisdiction over human cells and tissues, but only with respect to allogeneic cells, which

"could be grown in large bioreactors and distributed to the public like a mass produced drug product." Michael Freeman & Michael Fuerst, *Does the FDA Have Regulatory Authority over Adult Autologous Stem Cell Therapies?*, J. TRANSLATIONAL MED., Mar. 26, 2012 at 1, 2. That all changed in 2006, when the FDA modified a single regulation, implemented without public notice and comment rulemaking. Before 2006, the FDA defined HCT/Ps in part to mean "any human tissue derived from a human body and intended for transplantation into *another* human." 21 C.F.R. § 1271.3(d)(1) (2005) (emphasis added). But in 2006, the FDA changed the definition to define HCT/Ps to mean "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into *a* human recipient." 21 C.F.R. § 1271.3(d) (2006) (emphasis added). With this subtle shift, the FDA unilaterally manufactured jurisdiction over a patient's autologous cells and tissues. *See* Chirba, 7 J. HEALTH & BIOMEDICAL L. at 254; *see also* Freeman, J. TRANSLATIONAL MED. at 2 ("For the first time, by nothing more than semantic sleight of hand, the agency bequeathed itself authority over a broad group of medical procedures[.]").

Thus, for over half a century, the FDA never claimed to have

jurisdiction over surgical procedures involving a patient's body parts. And even when the FDA did start regulating HCT/Ps, it did so under the PHSA and disclaimed any intention to regulate autologous surgical procedures. The FDA's newfound assertion of power over a physician's use of autologous cells and tissues to treat disease thus warrants a "measure of skepticism." *Util. Air*, 573 U.S. at 324.

4. There Is a Mismatch Between the FDA's Asserted Jurisdiction and Its Congressionally Assigned Mission and Expertise.

Fourth, critical judicial examination of an agency's assertion of jurisdiction "may be merited when there is a mismatch between an agency's challenged action and its congressionally assigned mission and expertise." *West Virginia*, 142 S. Ct. at 2623 (Gorsuch, J., concurring). Such a mismatch exists here. The FDA has expertise over protecting consumers from unsafe and ineffective drugs (*see* 21 U.S.C. § 393(b)(2)), but it does not have expertise over the regulation of medical surgeries.

In the context of mass-produced drugs, there is an inherent information asymmetry that exists between the drug manufacturer and the consumer. The FDCA's adulteration, misbranding, and pre-market testing standards address this asymmetry by assuring consumer risks associated

with an approved medicine are acceptably low. *See* Freeman, J. TRANSLATIONAL MED. at 2.

Surgery involving autologous tissues and cells is different. In that circumstance, the risk of information asymmetry is addressed through the process of informed consent, which ensures that the patient understands the relevant benefits and risks necessary to make an informed decision about the use of his own body parts. *Id.* It is not reasonable to believe that Congress intended for the physician/patient relationship to be regulated in the same way as a drug manufacturer. Rather, the risks of ordinary surgical procedures fall squarely within the ambit of state public health authorities' expertise. *See* Richard A. Epstein, *The FDA's Misguided Regulation of Stem-Cell Procedures*, Sept. 2013 at 1, 15. For this reason as well, the FDA's cryptic definition of "drug" does not provide clear congressional authorization to regulate a patient's own cells and tissues.

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In sum, asking the questions posed by the Major Questions Doctrine yields a clear answer: the FDCA does not authorize the FDA to regulate a physician's use of a patient's own stem cells to treat disease. The FDA thus lacks jurisdiction to regulate Appellees' SVF Surgical Procedure and

Expanded MSC Surgical Procedure.[4]

II. APPELLEES' SVF SURGICAL PROCEDURE QUALIFIES FOR THE SAME SURGICAL PROCEDURE EXCEPTION.

Even if the FDA had jurisdiction to regulate the SVF Surgical Procedure, the procedure would be, as the district court correctly concluded, exempted by the Same Surgical Procedure Exception set forth in 21 C.F.R. § 1271.15(b). 1-ER-17. The government's contrary argument is based on a misreading of the exception's plain terms and violates several canons of construction.

A. The Same Surgical Procedure Exception.

Because surgical procedures involving implantation of autologous tissue pose a low risk of communicable disease, the FDA has exempted from oversight any "establishment that removes HCT/P's from an

[4] The district court found that the government presented no evidence that Defendants adulterated or mislabeled any material in connection with the Expanded MSC Surgical Procedure. 1-ER-10-11. The government does not contest these findings on appeal. Accordingly, even if the Expanded MSC Surgical Procedure were to constitute a "drug," the district court should be affirmed with respect to the Expanded MSC Surgical Procedure because adulteration and misbranding is an essential element of the government's claim. *See* 1-ER-18; *see also MacKay v. Pfeil*, 827 F.2d 540, 542 n.2 (9th Cir. 1987) (failure of a party in its opening brief to challenge an alternative ground for a district court's ruling given by the district court waives that challenge).

individual and implants such HCT/P's into the same individual during the same surgical procedure." 21 C.F.R. § 1271.15(b).

There is no dispute that Appellees' SVF Surgical Procedure removes and implants cells into the same individual from whom they were removed during the same surgical procedure. The dispute thus turns on whether Appellees remove HCT/Ps and reimplant "*such* HCT/P's." As the district court found, and as Appellees detail below, the SVF Surgical Procedure falls within the SSP exception.

B. Appellees Implant the Same Cells Into Patients in the Same Surgical Procedure.

Appellees' SVF Surgical Procedure qualifies under the unambiguous terms of the SSP exception because Appellees remove cells from a patient and then reimplant the same cells back into the patient. That conclusion follows from a straightforward analysis of the two words at issue: "such" and "HCT/P's."

1. Cells Are an HCT/P for Purposes of the SSP Exception.

"HCT/P" is an acronym for "[h]uman cells, tissues, or cellular or tissue-based products." 21 C.F.R. § 1271.3(d). But not any cell or tissue qualifies as an HCT/P. Rather, HCT/Ps are limited to those "articles

containing or consisting of human cells or tissues" that are "intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 C.F.R. § 1271.3(d).

On appeal, the government argues that adipose tissue is the *only* HCT/P relevant to the analysis because it is the largest system removed. *See* AOB 27. But that is wrong as a matter of plain language. Adipose tissue is *one* HCT/P involved in the SVF Surgical Procedure, because it is an "article[] *containing* … human cells … that are intended for implantation." But the stem cells are themselves *another* HCT/P because they are "articles … *consisting* of human cells … that are intended for implantation." *See* 1-ER-31 ("The parties agree that both adipose tissue and SVF cells are HCT/P's[.]"). The government ignores the fact that, by using the disjunctive *or*, § 1271.3(d)'s definition of HCT/P contemplates that *either* tissues *or* cells may be considered HCT/Ps for purposes of the SSP exception. *See United States v. Gallegos*, 613 F. 3d 1211, 1215 (9th Cir. 2010) ("We have consistently defined 'or' as indicating separate alternatives."); *Azure v. Mortone*, 514 F.2d 897, 900 (9th Cir. 1975) ("As a general rule, the use of a disjunctive in a statute indicates alternatives and requires that they be treated separately.").

The SSP exception applies, therefore, if Appellees reimplant *either* "such" adipose tissue *or* "such" cells contained in the adipose tissue back into the patient. The government is wrong to suggest this Court must choose one or the other as the relevant HCT/P before analyzing the SSP exception.

But even if such a choice were required, "a characterization that focuses on the target of removal is more reasonable than one that includes everything that was removed." 1-ER-33. This is because the term "HCT/P" is defined according whether the human cells or tissues are "intended for implantation." 21 C.F.R. § 1271.3(d). Here, only the SVF cells which reside in the adipose tissue are intended to be implanted.

Moreover, and as explained more fully *infra* at Part II.D.2, a characterization that focuses on the largest system removed creates surplusage by reading cells and cellular-based products out of the SSP exception entirely. *See* 1-ER-32. Cells can only be removed with the tissues that surround them. Therefore, a focus on the largest system removed would mean "cells" and "cellular-based systems" as used in the definition of HCT/P could *never* be HCT/Ps. This defies logic.

2. "Such" Cells Means the Same Cells Just Removed.

Because a patient's cells can be HCT/Ps under the SSP exception, the exception applies so long as Appellees reimplant "such" cells into the same patient in the same procedure. The word "such" is unambiguous. 1-ER-31. In legal parlance, "such" refers to an antecedent: "[t]hat or those; having just been mentioned." *Such*, BLACK'S LAW DICTIONARY (11th ed. 2019). Thus, the SSP exception requires only that the HCT/P Appellees reimplant—*i.e.*, the stem cells—be the same stem cells that were removed from the patient. 1-ER-31.

By way of contrast, a physician would not qualify for the SSP exception if she removed tissues and cells from a patient and then reimplanted a different article into the patient, say a donated organ. Nor would a physician likely fall under the SSP exception if they took cells from a patient and then spliced the DNA in the cells. Arguably, those new cells are different HCT/Ps. *See* 1-ER-31.

But this case does not fall at the margins. As the district court found, the cells Appellees remove from a patient "are not altered, chemically or biologically, at any point during the SVF Surgical Procedure." 1-ER-8 ¶ 17. The district court's uncontested finding is well-supported by the trial

record.[5] *See, e.g.*, 8-ER-1173-1175. And it follows from this finding that because Appellees remove and reimplant the *same* unaltered stem cells back into a patient during the same procedure, the SVF Procedure falls within the SSP exception.

C. The District Court's Conclusion that the Same Surgical Procedure Exception Applies to the SVF Surgical Procedure Is Supported by the History and Purpose of the HCT/P Regulations.

The district court followed this straightforward approach in concluding that the SSP exception applies. 1-ER-32. Contrary to the government's assertion (AOB 28-31), the history and purpose of the HCT/P regulations support the district court's judgment.

1. The District Court's Interpretation Is Consistent with the SSP Exception's History.

The SSP exception originally was drafted to exempt establishments that remove "human cells or tissues or any cell or tissue-based component" from an individual "and implant such cells or tissues into the same individual during the same surgical procedure." 63 Fed. Reg. at 26754.

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[5] *Amici* for the government dispute this factual finding, arguing that "[i]solated SVF cells are … widely viewed as being biologically different from normal cells within adipose tissue." Amicus Br. at 24. However, in support of this proposition, *Amici* cites the deposition of a government witness whom the district court found not credible. *See id.* (citing 1-SER-8-9 ¶ 16); 1-ER-16.

Under this original version, there can be no serious dispute that Appellees would qualify for the SSP exception: they remove human cells and implant such cells into the same individual during the same surgical procedure. While the SSP exception as enacted is slightly different, the regulatory history confirms that the revised language was intended to have a similar "scope" and had nothing to do with incorporating some sort of "original form" requirement into the SSP exception. *See* 66 Fed. Reg. at 5455.

2. The District Court's Interpretation Is Consistent with the SSP Exception's Purpose.

The district court's interpretation also is consistent with the purpose of the HCT/P regulations as a whole. The HCT/P regulations adopted "a tiered approach to cell and tissue regulation." 1997 Proposed Approach at 6. Keeping in mind that the HCT/P regulations are issued under the PHSA, which authorizes the FDA to regulate communicable diseases, the purpose of this tiered approach was to "prevent the introduction, transmission, and spread of communicable diseases by HCT/P's." 66 Fed. Reg. at 5467.

In establishing these tiers, the FDA distinguished "between cellular and tissue-based products for which the agency would not require

communicable disease-controls" and "products for which it would require communicable-disease controls." 1997 Proposed Approach at 12. With respect to the former category, the FDA announced that it "would not assert any regulatory control over cells or tissues that were removed from a patient and transplanted back into that patient during a single surgical procedure." *Id.* The FDA justified this same surgery exception on two grounds.

First, "autologous use of cells and tissues raises lesser communicable-disease concerns than does allogeneic use." *Id.* at 13. The use of allogenic HCT/Ps increases the risk of transmitting a communicable disease, "because the donor from whom the cells or tissue was obtained could carry an infectious agent to which the recipient is susceptible." *Id.* at 12. *Second*, by requiring that the HCT/P be implanted in the same surgical procedure, the SSP exception avoids any risks associated with storing HCT/Ps. "Storage in the same location as other human cellular or tissue-based products gives rise to concerns about the spread of infectious disease" and for that reason the SSP exception is limited to HCT/Ps that are implanted in the same surgical procedure or quarantined pending completion of the surgery. 63 Fed. Reg. at 26748.

The district court's interpretation of the SSP exception is faithful to both rationales. The risk of communicable disease is low when a patient receives his own stem cells because there is no risk of donor-infection and a limited risk of infection from HCT/Ps of other patients.

3. The Government's Critique of the District Court's Interpretation Is Based on a Misreading of Its Own Regulations.

The government argues that the district court's interpretation is inconsistent with the history and purpose of the SSP exception in two respects. Neither is persuasive.

First, the government argues that for the SSP exception to apply, the safety and effectiveness risks must "generally … [be] no different from those typically associated with surgery." AOB 12 (quoting 1997 Proposed Approach at 12); AOB 30. The government contends the SVF Surgical Procedure "pose[s] risks to patient health and safety that are qualitatively different from, and greater than, those typically associated with surgery." AOB 30.

But as noted, the purpose of the HCT/P regulations is to prevent the spread of *communicable* diseases. 66 Fed. Reg. at 5467. Thus, the government's focus on alleged complications is a red herring. *See* AOB 11-

12, 30-31. None of those supposed complications has anything to do with the transmission of communicable diseases.[6]

In any event, the district court declined to adopt the government's contention that the SVF Surgical Procedure poses "significant risks to the consumers" who receive the treatment. 1-SER-139 ¶ 102. It must therefore be presumed the district court rejected this argument. *Bennett v. Islamic Republic of Iran*, 825 F.3d 949, 962 (9th Cir. 2016); *W. Pac. Fisheries, Inc. v. SS President Grant*, 730 F.2d 1280, 1285 (9th Cir. 1984). Rightly so. A government witness testified about a purported theoretical risk of blood clots and pulmonary embolism, but she never demonstrated that Appellees' patients developed such symptoms. *See* AOB 11 (citing 5-ER-539-540). And while the government claims to identify examples of patients "suffering serious complications" after undergoing Appellees' treatments, the actual evidence is to the contrary. *See* 10-ER-1515-1519

[6] *Amici* for the government assert that implantation of stem cells has "resulted in patients being … infected with dangerous pathogens." Amicus Br. at 14-15. But the article *Amici* cite concerned umbilical cord blood-derived stem cells from a donor, *not* autologous use. *See* Kiran M. Perkins, et al., *Notes from the Field: Infections After Receipt of Bacterially Contaminated Umbilical Cord Blood-Derived Stem Cell Products for Other Than Hematopoietic or Immunologic Reconstitution*, 67 MORBIDITY & MORTALITY WKLY. REP. 1397, 1397 (2018).

(finding *no* evidence swelling was caused by SVF treatment, rather than other treatments received by patient); *see also* 8-ER-1134-1135 (patient suffered retinal detachment when affiliate physician—not Appellees—deviated from protocol). Conversely, there was ample evidence that Appellees' SVF Surgical Procedure is safe and poses no more risk than typical surgery. *See, e.g.*, 5-ER-607-612; 5-ER-620-723; 1-SER-218-220.

Second, the government argues that exempting Appellees' procedure from oversight contravenes the FDA's intention to subject cells that are extensively manipulated to regulation. AOB 31. The government's argument misses the mark.

When adopting the HCT/P regulations, the FDA observed that "[i]mproper handling" can alter or destroy the integrity or function of cells and cause them to become contaminated. 1997 Proposed Approach at 15. Even so, the FDA announced that "[a]utologous use of cells and tissues harvested and transplanted in a single surgical procedure" would *not* be subject to FDA handling and processing controls. *Id.* The risks of transmitting communicable disease because of processing warrants FDA oversight only if the cells are not reimplanted in a single surgical procedure. *Id.*; *see also id.* at Table 1, Row B1 (cells removed from and

transplanted back into the same person in the same surgical procedure not subject to processing controls).

The preamble to the FDA's 2001 final rule on HCT/Ps cited by the government proves the point. *See* AOB 31. In that preamble, the FDA explained that when a hospital does *not* use cells or tissues in the same surgical procedure, a hospital may still qualify for the exception by storing autologous tissue for use in a future surgical procedure "so long as the hospital does not engage in any other activity encompassed with in the definition of 'manufacture.'" 66 Fed. Reg. at 5460. The natural implication of this comment is self-evident: if a physician *does* implant the autologous tissue or cells in the same surgical procedure, any processing of that HCT/P is irrelevant.

D. The Government's Interpretation of the SSP Exception Is Legally Untenable.

In contrast to the district court's interpretation, which accords with the plain language, history, and purpose of the HCT/P regulations, the government's own interpretation violates several canons of construction.

1. The Government's Interpretation Violates the Ordinary Meaning Canon.

To begin, the government's interpretation of the SSP exception

violates the principle that words are to be understood in their ordinary, everyday meanings. *See New Prime Inc. v. Oliveira*, 139 S. Ct. 532, 539 (2019).

According to the government, an HCT/P remains "such HCT/P" only when "it is in its original form." 2017 Guidance at 5. And that means "the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleansing, sizing, and shaping." *Id.* This, then, is the upshot of the FDA's interpretation—"such" does not mean aforementioned, as recognized by dictionaries. It means "in its original form, which allows only for rinsing, cleansing, sizing, and shaping." Put simply, the government is not asking this Court to *interpret* the word "such," but to impermissibly *rewrite* it. *See Fina Oil & Chem. Co. v. Norton*, 332 F.3d 672, 676 (D.C. Cir. 2003) (agencies cannot circumvent the notice-and-comment process "by rewriting regulations under the guise of interpreting them").

Moreover, it "makes no logical sense" to interpret the word "such" to allow "physical cutting" of tissue, but not the "chemical cutting" of tissue at issue here. 1-ER-33 n.14. The acts permitted by the government's interpretation—sizing and shaping—will, of course, remove some of the

cells from the tissue. 1-SER-247-248. Yet the government proffered no evidence that the *form* of cutting has any impact on the risk of communicable disease; rather, it is the *type* of tissue that matters, *i.e.*, autologous or allogenic. The FDA's *sui generis* dichotomy thus finds no footing in § 1271.15's mere use of the word "such."

2. The Government's Interpretation Violates the Surplusage Canon.

The government's interpretation of the SSP exception is also untenable because it unnecessarily creates surplusage. *United States v. Rangel-Gonzales*, 617 F.2d 529, 533 (9th Cir. 1980).

According to the government, the SSP exception focuses on "the largest system that was removed"—here, a patient's adipose tissue. 1-ER-32. The problem with the government's construction is that the term HCT/P includes *either* human cells *or* tissues. 21 C.F.R. § 1271.3(d). Cells "can only be removed from a patient along with larger systems, such as the tissues or organs that they comprise." 1-ER-16. If the FDA were correct, and the SSP exception demanded the removal to be characterized by the largest system that was removed, then "it could never be applied to the removal and implantation of a cell." 1-ER-32. For purposes of the SSP

exception, the government's interpretation thus would read the cells out of the HCT/P definition altogether. *Id.*

To this, the government raises a factual challenge, arguing that there is one example of a human cell that can be removed in isolation: human ovocytes. AOB 34-35. But that trial testimony, provided by one of the government's witnesses, contradicted the witness' own deposition testimony. 6-ER-767. And contrary testimony established that cells can only be removed from an individual along with larger systems, such as the tissues or organs that they comprise.[7] 7-ER-944; 1-ER-17 (finding Appellees' evidence more credible than the government's expert). The government does not explain how the district court committed clear error by accepting one conflicting account over another. *See United States v. Frank*, 956 F.2d 872, 875 (9th Cir. 1991) ("Clear error is not demonstrated by pointing to conflicting evidence in the record.").

The government also raises a legal objection, arguing the district court's interpretation violates the canon against superfluity by reading the

[7] At the least, the government proffered *no* evidence that removing an isolated cell was possible when § 1271.3(d) was promulgated in 2004.

word "tissues" out of § 1271.3(d). AOB 35-36. But the government is wrong. "An interpretation of the SSP Exception that focuses on the target of the removal and implantation gives effect to both 'tissue' and 'cell' as some procedures target tissues and others target cells." 1-ER-32.

3. The Government's Interpretation Improperly Imports a Minimal Manipulation Requirement from a Different Regulation.

The FDA's interpretation should be rejected also because it contravenes the principle that a negative inference may be drawn from the exclusion of language from one regulatory provision that is included in related regulations. *Russello v. United States*, 464 U.S. 16, 23 (1983); *Mountain Communities for Fire Safety v. Elliott*, 25 F.4th 667, 676 (9th Cir. 2022).

Separate and apart from the SSP exception, the FDA's HCT/P regulations subject so-called "minimally manipulated" HCT/Ps to a lighter regulatory burden. Under this provision, an HCT/P is subject to lighter regulation if, *inter alia*, it is "minimally manipulated" (21 C.F.R. § 1271.10(a)(1)), which means that any processing cannot "alter the relevant biological characteristics of cells or tissues." 21 C.F.R. § 1271.3(f)(2).

Critically, the SSP exception does *not* include a minimal manipulation

requirement. Yet the government would have "such HCT/P" graft onto the SSP exception a manipulation requirement. Specifically, the government argues that "the only processing steps that will allow an HCT/P to remain 'such HCT/P' are rinsing, cleansing, sizing, and shaping." AOB 39.

The FDA has it backwards. The exclusion of a minimally manipulated requirement in the SSP exception suggests, by negative implication, that the SSP exception should not turn on the extent to which an HCT/P is manipulated. *Quebrado Cantor v. Garland*, 17 F.4th 869, 874 (9th Cir. 2021). To be sure, the surgeon must remove and reimplant the same cells or tissues but limiting the exception to situations in which the physician does no more than rinse, clean, size, and shape an HCT/P improperly imports manipulation principles from § 1271.10 into § 1271.15.

According to the government, Appellees' interpretation leads to a "strange" result: stem cells, despite having been manipulated too much to qualify for the lower tier of regulation, would be exempt altogether under the same surgical procedure exemption. AOB 29. To begin, the government is wrong to assume that Appellees' SVF Surgical Procedure does not meet the minimal manipulation requirement. A cell is "minimally

manipulated" if processing of the cell does not alter its relevant biological characteristics. *See* 21 C.F.R. § 1271.3(f)(2). Here, the district court found that the SVF procedure does *not* alter the stem cells' biological characteristics. 1-ER-8; *compare with Regenerative Sciences*, 741 F.3d at 1322 (rejecting application of the minimal manipulation exception because the defendants added substances that affected the cells' biology).

Regardless, it is not strange at all that some procedures would be exempted under the SSP exception, even if they would not qualify for the minimal manipulation exemption. The minimal manipulation exemption is available to establishments that transfer HCT/Ps from one donor to a different recipient. *See* 21 C.F.R. § 1271.10(a)(4)(i). The FDA has long recognized that "[t]he use of allogeneic rather than autologous cellular or tissue-based products increases the risk of transmission of communicable disease, because the donor from whom the cells or tissue was obtained could carry an infectious agent to which the recipient is susceptible." 1997 Proposed Approach at 12. For that reason, the HCT/P regulations consistently subject autologous tissue and cell transfers to lesser restrictions. *See, e.g.*, 21 C.F.R. § 1271.90(a)(1); *id.* § 1271.90(c)(3); *id.* § 1271.55(a)(1). It is thus the government's position that would lead to

bizarre results by subjecting autologous tissue and cell transfers to stricter restrictions than allogeneic transfers.

4. The Government's Reliance on *US Stem Cell* is Misplaced.

Finally, the government's reliance on *US Stem Cell*, 998 F.3d at 1310, is misplaced because that decision rests on several legal missteps.

The court began by concluding that both adipose tissue and the stem cells they contain can be HCT/Ps for purposes of the SSP exception. *See US Stem Cell*, 998 F.3d at 1308. The court reasoned that because HCT/Ps are defined as "articles *containing* or *consisting of* human cells or tissues that are intended for implantation," both adipose tissue (which *contains* the cells intended to be transplanted) and the cells themselves (which *consist* of cells) qualify as HCT/Ps. *Id.*

But the court then failed to consider whether the defendants could satisfy the SSP exception by reimplanting *either* such cells or such adipose tissue. Instead, without explanation, the court accepted the government's position that the SSP exception can only refer to one or the other. This was error. *See supra* Part II.B.1.

The court's next misstep was to defer to FDA guidance documents without first determining whether the text of the SSP exception was

ambiguous so as to require deference. *See US Stem Cell*, 998 F.3d at 1309. Despite noting that the government's characterization of "such HCT/P's" reads cells out of the HCT/P definition, the Eleventh Circuit never resolved that interpretive dilemma. *See id.* Nor did the court ever confront the fact that the government's "original form" requirement is untethered from the text of the SSP exception, or how the requirement results in a foundationless and unreasonable dichotomy between surgeries involving physical cutting and those involving chemical cutting. For all the reasons explained above, basic canons of construction preclude the FDA from incorporating an "original form" requirement into the SSP exception.

E. The FDA's Interpretation of the SSP Exception Is Not Entitled to Deference.

Ultimately, the government retreats to a request for deference under *Kisor*, a "maimed and enfeebled" form of deference. 139 S. Ct. at 2425 (Gorsuch, J., concurring). *Kisor* deference can arise only if a regulation is "genuinely ambiguous, even after a court has resorted to all the standard tools of interpretation." *Id.* at 2414. Even then, "the agency's reading must still be 'reasonable.'" *Id.* at 2415. Moreover, courts will not defer to agency interpretations unless they reflect "authoritative" action and do not create

"unfair surprise" to regulated parties. *Id.* at 2416-18. The agency's plea for deference fails each of these requirements.

First, the SSP exception is not ambiguous, as both parties agree. *See* 1-SER-42; 1-SER-118. A commonsense, dictionary-based definition of "such HCT/P" means the same HCT/Ps that were removed from the patient in a single procedure. 1-ER-31.

Second, the government's interpretation is unreasonable. The FDA seeks to replace the words "such HCT/P" with the phrase "HCT/P's in their original form, with processing limited to rinsing, cleansing, sizing, or shaping." 2017 Guidance at 5. This is not mere interpretation; it is revision by fiat. *See Util. Air*, 573 U.S. at 328 (reaffirming the "core administrative-law principle that an agency may not rewrite clear" terms "to suit its own sense of how" a law "should operate").

Third, the FDA's interpretation is not entitled to deference because it is predicated upon a 2017 guidance document that does not "make authoritative policy in the relevant context." *Kisor*, 139 S. Ct. at 2416. On its face, the 2017 guidance "does not establish any rights for any person and is not binding on FDA or the public." 2017 Guidance at 1. FDA guidance documents "should be viewed only as recommendations" and

"do not establish any legally enforceable responsibilities." *Id.* at 2. Given that the FDA disclaimed any binding force of the guidelines, they are not entitled to *Kisor* deference. *See Exelon Generation Co., LLC v. Loc. 15, Int'l Bhd. of Elec. Workers, AFL-CIO*, 676 F.3d 566, 577 (7th Cir. 2012).

CONCLUSION

For these reasons, the judgment of the district court should be affirmed.

July 26, 2023

Respectfully submitted,

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STATEMENT OF RELATED CASES

Pursuant to Ninth Circuit Rule 28-2.6, Appellees state that they are not aware of any related cases pending before the Court.

July 26, 2023

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CERTIFICATE OF COMPLIANCE

This brief complies with the length limits permitted by Ninth Circuit Rule 32-1. The brief is 13,984 words, excluding the portions exempted by Federal Rule of Appellate Procedure 32(f). The brief's type size and type face comply with Federal Rule of Appellate Procedure 32(a)(5) and (6).

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